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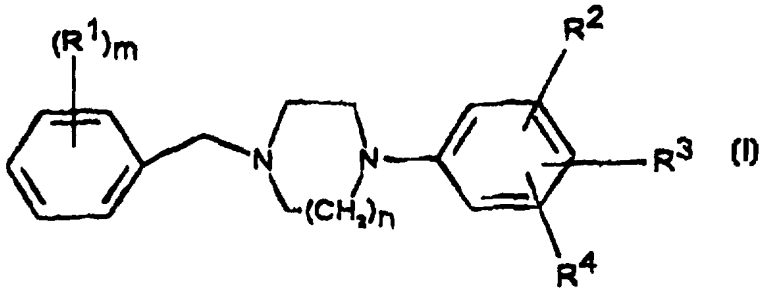
(54) Title: NOVEL PIPERAZINE OR HOMOPIPERAZINE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME AND A PROCESS FOR THEIR PREPARATION

(57) Abstract

The invention refers to novel piperazine and homopiperazine derivatives of formula (I) being suitable for the treatment of dieseases due to pathological alterations of the central nervous system, pharmaceutical compositions containing the above derivatives, and a process for the preparation of the novel compounds. In formula (I) R^1 stands for a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trihalomethyl group, a nitro group or an amino group which latter can be substituted by a C_{1-4} alkyl group, and n has a value of 1 or 2, or R^1 represents a cyano group, and n has a value of 2, m is 0, 1, 2 or 3, R^2, R^3 and R^4 mean, independently, a hydrogen, a halo, a trihalomethyl group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a nitro group, a carboxy group, a formyl group, a hydroxy group or an amino group which latter can be substituted by a C_{1-4} alkyl group.



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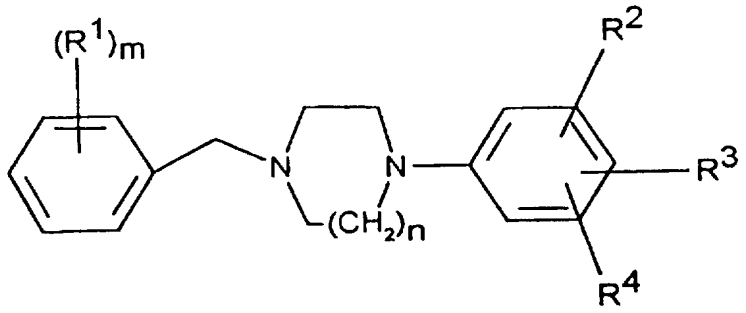
NOVEL PIPERAZINE OR HOMOPIPERAZINE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME AND A PROCESS FOR THEIR PREPARATION

The invention refers to novel piperazine or homopiperazine derivatives, pharmaceutical compositions containing the same, a process for the preparation of the novel compounds, a medical process using the novel compounds and novel intermediates useful in the preparation of the above piperazine or homopiperazine derivatives.

More specifically, the invention refers to novel piperazine and homopiperazine derivatives of the formula



I

wherein

R^1 stands for a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trihalomethyl group, a nitro group or an amino group which latter can be substituted by a C_{1-4} alkyl group, and

n has a value of 1 or 2, or

R^1 represents a cyano group, and
n has a value of 2,
m is 0, 1, 2 or 3,
R^2, R^3 and R^4 mean, independently, a hydrogen, a halo, a trihalomethyl group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a nitro group, a carboxy group, a formyl group, a hydroxy group or an amino group which latter can be substituted by a C_{1-4} alkyl group,
and pharmaceutically acceptable acid addition salts thereof.

The novel compounds of the formula I are suitable, in the first place, for the treatment of diseases of the central nervous system.

Several 1,4-disubstituted piperazine derivatives are known from the literature.

1-Phenyl-4-(hydroxymethylbenzyl)piperazine derivatives having antipsychotic activity are known from the published European Patent Application No. 574 271. In Example 6, the starting compound is 1-(3-cyanobenzyl)--4-(2-methoxyphenyl)piperazine.
1-(2-Hydroxy-3,4-dimethoxybenzyl)-4--phenylpiperazine derivatives known from the published European Patent Application No. 617 027 are suitable for the treatment of diseases accompanied by the acute or chronic oxidative damage of the central nervous system. These compounds are claimed to give protection especially against the brain catastrophes of aged people.

1-Phenyl-4-(aminocarbonyl- or aminosulfonylbenzyl)piperazine derivatives having antipsychotic activity are described in PCT Applications published under numbers WO 93/04684 and WO 93/04682.

From the PCT Application published under No. WO 94/06768 1-phenyl-4-(methylbenzyl)-piperazine - the methyl group of which is substituted by a heteroring containing nitrogen - having antipsychotic activity is known.

The known antipsychotic piperazine derivatives are characterized by a usual dopamin (D_2) antagonist activity.

The aim of the invention is to prepare novel piperazine derivatives that influence the central nervous and peripheral neurotransmitter system.

It was found that the above aim was achieved by the novel piperazine and homopiperazine derivatives of the formula I.

In the description, a C_{1-4} alkyl group is a methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, tert.butyl or isobutyl group. Preferably, a C_{1-4} alkyl group is a methyl group.

A C_{1-4} alkoxy group is generally a methoxy, ethoxy, n-propoxy or n-butoxy group, preferably a methoxy group.

In general, a halo is a fluoro, chloro or bromo, preferably chloro or fluoro.

If m has a value of 0, hydrogen atoms

are bonded to the carbon atoms of the benzyl group which are substituted by R^1.

If n has a value of 1, the compound of the formula I is a piperazine derivative. If n has a value of 2, the compound of the formula I is a homopiperazine derivative. In general, the compounds of the formula I are called as piperazine derivatives, however, homopiperazine derivatives are included, too.

A preferred sub-group of the piperazine derivatives of the formula I consists of the compounds of the formula I, wherein

R^1 stands for a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a nitro group or a trifluoromethyl group,

m is 0, 1 or 2,

R^2, R^3 and R^4 represent, independently, a hydrogen, a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trifluoromethyl group, a nitro group, an amino group, a formyl group or a carboxy group,

n is 1 or 2,

and pharmaceutically acceptable acid addition salts thereof.

Suitable piperazine derivatives of the formula I consist of the compounds wherein in formula I

R^1 stands for a chloro, a fluoro, a methyl group, a methoxy group, a nitro group or a trifluoromethyl group,

m is 0, 1 or 2,

R^2, R^3 and R^4 represent, independently, a

hydrogen, a chloro, a methyl group, a methoxy group, a trifluoromethyl group, a nitro group, an amino group, a formyl group or a carboxy group,

n is 1 or 2,

and pharmaceutically acceptable acid addition salts thereof.

Specifically preferred compounds of the invention consist of piperazine derivatives of the formula I wherein

R^1 stands for a chloro, a fluoro, a methyl group or a methoxy group,

m is 0 or 1,

R^2, R^3 and R^4 represent, independently, a hydrogen, a chloro, a methyl group, a methoxy group, a trifluoromethyl group, a nitro group, an amino group or a formyl group,

n is 1,

and pharmaceutically acceptable acid addition salts thereof.

Preferred representatives of the compounds of the formula I are as follows:

1-benzyl-4-(5-amino-4-methyl-2-nitrophenyl)-piperazine dihydrochloride;

1-(4-chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;

1-(2-chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;

1-(3-chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;

1-(3-methoxybenzyl)-4-(5-amino-4-methyl-2-

-nitrophenyl)piperazine dihydrochloride;
1-(4-methylbenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine hydrochloride;
1-(2-methylbenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)-piperazine hydrochloride;
1-(2-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-(3-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-(4-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-benzyl-4-(2,5-diamino-4-methylphenyl)-piperazine trihydrochloride;
1-benzyl-4-(2-formyl-3-chlorophenyl)piperazine;
1-(4-methyl-3-nitrobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-(2,6-dichlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-(2-fluoro-chlorobenzyl)-4-(5-amino-4-methyl--2-nitrophenyl)piperazine dihydrochloride monohydrate;
1-benzyl-4-(5-amino-4-methyl-2-nitrophenyl)-homopiperazine dihydrochloride;
1-(4-chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride;
1-benzyl-4-(4,5-dimethoxy-2-nitrophenyl)-piperazine;
1-(2-chlorobenzyl)-4-(4,5-dimethoxy-2-nitrophenyl)piperazine;
1-(2-fluorobenzyl)-4-(4,5-dimethoxy-2-nitrophenyl)piperazine;
1-(3-methoxybenzyl)-4-(5-amino-4-methyl-2-

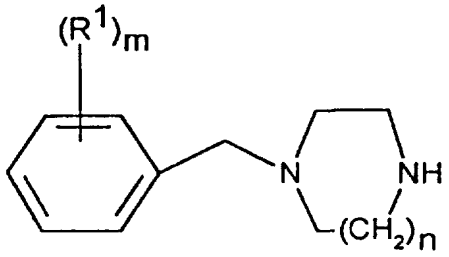
-nitrophenyl)homopiperazine dihydrochloride;
1-(4-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride;
1-(2-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride;
1-(3-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride;
1-(3-trifluoromethylbenzyl)-4-(5-amino-4--methyl-2-nitrophenyl)homopiperazine dihydrochloride.

Specially preferred representatives of the compounds of the formula I are as follows:
1-benzyl-4-(5-amino-4-methyl-2-nitrophenyl)-piperazine dihydrochloride;
1-(4-chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-(3-chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-(2-chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-(3-methoxybenzyl)-4-(5-amino-4-methyl-2--nitrophenyl)piperazine dihydrochloride;
1-(4-methylbenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine hydrochloride;
1-(2-methylbenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine hydrochloride;
1-(2-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-(3-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;
1-(4-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride;

1-benzyl-4-(2-amino-4-trifluoromethylphenyl)-piperazine dihydrochloride;
1-benzyl-4-(2-formyl-3-chlorophenyl)piperazine;
1-benzyl-4-(5-amino-4-methyl-2-nitrophenyl)-homopiperazine dihydrochloride;
1-(4-fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride.

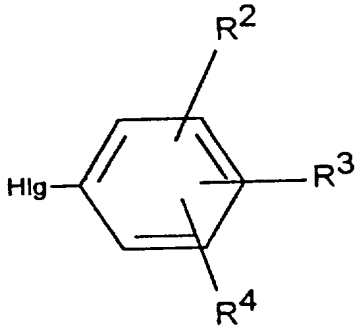
According to the invention, the compounds of the formula I are prepared as follows:

a) a 1-benzylpiperazine derivative of the formula



II

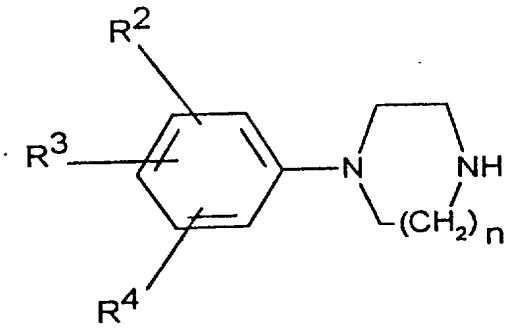
wherein R^1, m and n are as stated above, is reacted with an aromatic halo compound of the formula



III

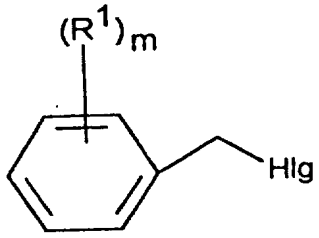
wherein R^2, R^3 and R^4 are as stated above, Hlg represents a chloro or bromo atom; or

b) a 1-phenylpiperazine derivative of the formula



IV

wherein R^2, R^3, R^4 and n are as stated above, is reacted with a benzyl halide of the formula



V

wherein R^1 and m are as stated above, Hlg represents a chloro or bromo atom;

and, if desired, an obtained compound of the formula I is converted to a pharmaceutically acceptable acid addition salt thereof;

or, if desired, an obtained compound of the formula I, wherein one or more of R^1, R^2, R^3 and R^4 stand(s) for a nitro group, m and n are as stated above, is catalytically hydrogenized to obtain a corresponding amino compound.

In case of process a), the 1-benzylpiperazine derivative of the formula II is reacted with the aromatic compound of the formula III in the presence of an acid binding agent. Preferred agents for this purpose are alkali metal carbonates such as sodium carbonate or potassium carbonate; alkali metal hydrocarbonates such as sodium or potassium hydrogen carbonate; alkali metal hydroxides such as sodium or potassium hydroxide; alkali earth metal hydroxides such as calcium hydroxide; or tertiary amines such as triethylamine. Preferably potassium or sodium carbonate is used as the acid binding agent.

A catalyst can be employed to accelerate the reaction. Alkali metal halides such as potassium iodide or sodium bromide can be used as the catalyst. It is preferred to perform the reaction in the presence of potassium iodide.

The reaction proceeds in the presence of a solvent or in the excess of the benzylpiperazine. Suitable solvents are aliphatic alcohols such as methanol, ethanol; aromatic hydrocarbons such as benzene, toluene; dialkylamines, preferably dimethylformamide; dialkylsulfoxides, preferably dimethylsulfoxide; acetonitrile; ethylene glycol dialkyl ethers, preferably methyl Cellosolve$^{(R)}$ i.e. 2-methoxyethanol; and water. Particularly preferred solvents consist of

dimethylformamide, ethanol and acetonitrile.

The reaction time is 5 to 60 hours depending on the reactivity of the starting compounds and the temperature employed. The reaction temperature is 40 to 150 °C, preferably 80 to 120 °C.

The starting compounds of the formulae II and III are used in an equimolar amount, or a high excess of benzyl piperazine is employed. The acid binding agent is used in an equimolar amount or in a molar excess for each mole of reaction partners. The catalyst is taken in a 0.1 to 0.2 molar equivalent quantity. It is preferred to use 0.1 molar equivalent of catalyst.

If the reaction is performed in the presence of an organic solvent, the inorganic salts precipitated are filtered, and the solvent is distilled off under reduced pressure from the filtrate to separate the compound of the formula I from the reaction mixture. The residue obtained is purified by crystallization or column or flash chromatography.

According to another method, the main part of the unreacted starting compound of the formula III or other by-products are crystallized by treating the distillation residue with isopropanol or a mixture of chloroform and methanol or hexane and ethyl acetate. The crystals formed are removed, the mother liquor is evaporated, and the

residue is purified by chromatography, preferably flash chromatography, or by recrystallization.

According to a further possibility, the reaction mixture or a partially evaporated residue thereof is poured onto water and the crude product that separates in the form of crystals is purified by one of the above methods.

According to a still further method, the reaction mixture is completely evaporated, and the residue is dissolved in a high amount of ethanol to prepare an acid addition salt. The salt of the starting compound as well as a great part of the contaminations remain dissolved in ethanol.

If the solvent used in the reaction consists of water, the crystal suspension is filtered while hot, the crystals are washed with hot water and purified as given above, if necessary.

In case of process b) of the invention, the 1-phenylpiperazine derivative of the formula IV is reacted with the benzylhalide of the formula V in the presence of an acid binding agent, too. The compounds listed in connection with process a) can be used as the acid binding agent.

The reaction is performed in the presence of a solvent. For this purpose, the solvents listed in process a) are suitable. The reaction temperature is 20 to 150 ^{o}C, preferably 25

to 80 °C. The reaction time is, in general, 4 to 20 hours, depending on the reactivity of the starting compounds and the reaction temperature employed.

The starting compounds of the formulae IV and V are reacted in an equimolar amount or a slight excess of the compound of the formula V is used. The acid binding agent is used in an equimolar amount or in a molar excess for each mole of reaction partners. To separate the reaction product formed, the inorganic salts precipitated are filtered and the solvent is removed by evaporation under reduced pressure. If required, the product is suspended in water, then filtered.

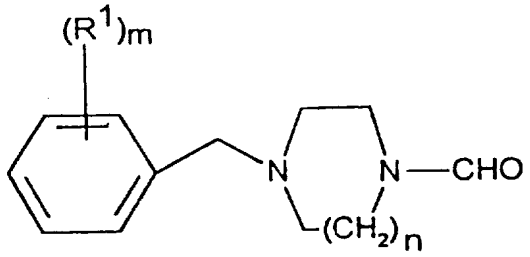
If desired, an obtained compound of the formula I is reacted with an inorganic or organic acid to form an acid addition salt. The salt formation is performed in a solvent, preferably ethanol, isopropanol or diethyl ether, under ice cooling, preferably at 0 to 55 °C, suitably with a tenfold excess of the acid that can be an inorganic acid such as hydrochloric acid, hydrogen bromide, sulfuric acid or phosphoric acid etc. or an organic acid such as acetic acid, maleinic acid, fumaric acid, oxalic acid etc.

If desired, a compound of the formula I, wherein one or more of R^1, R^2, R^3 and R^4 stand(s) for a nitro group, m and n are as stated relative to formula I, or an acid addition salt thereof is catalytically

hydrogenized to obtain a corresponding amino compound of the formula I.

The hydrogenization reaction is performed in an autoclave using a solvent. Suitable solvents are alcohols such as methanol, ethanol, isopropanol; aliphatic esters such as ethyl acetate; chlorinated aliphatic hydrocarbons such as chloroform or dichloroethane. The nitro compound of the formula I is hydrogenized with hydrogen gas in the presence of a catalyst, preferably platinum, palladium, platinumoxide or Raney nickel. It is preferred to use a palladium catalyst of the type Selcat Q, for example in an amount of 1 to 10 % by mass. The reaction is performed under a hydrogen pressure of (3 to 10)x10^5 Pa, suitably about 5x10^5 Pa. The reaction temperature is 20 to 50 ^oC, preferably room temperature. To separate the reaction product, at the end of the hydrogenization, the catalyst is removed by filtration, and the filtrate is transferred to a solvent that can contain an acid. According to an alternative method, the amine obtained is purified by flash chromatography, then converted to an acid addition salt as described above.

The monosubstituted benzylpiperazine derivatives of the formula II can be prepared either by the analogy of the method described in Journal of Medicinal Chemistry, 35, 2690 (1992) from the compounds of the formula



VI

wherein R^1, m and n are as defined above, by acidic hydrolysis, or from benzyl-(ethoxycarbonyl)piperazines by alkaline hydrolysis.

The compounds of the formula VI are prepared by reacting a benzylhalide of the formula V with 1-formylpiperazine or 1-formylhomopiperazine.
Benzyl-(ethoxycarbonyl)piperazines are commercially available.

The novel 1-benzyl-4-formylpiperazine derivatives of the formula VI, wherein
R^1 stands for a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trifluoromethyl group or a nitro group,
m is 0, 1, 2 or 3,
n is 1 or 2,
are valuable intermediates in the preparation of the compounds of the formula I, thus, the invention includes these compounds, too.

Representatives of the novel 1-formyl-4-benzylpiperazine derivatives of the formula VI are as follows:
1-formyl-4-(2-, 3- or 4-chlorobenzyl)-piperazine;

1-formyl-4-(2-, 3- or 4-trifluoromethyl-benzyl)piperazine;
1-formyl-4-(2-, 3- or 4-methylbenzyl)-piperazine;
1-formyl-4-(2-, 3- or 4-fluorobenzyl)-piperazine;
1-formyl-4-(2,6-dichlorobenzyl)piperazine;
1-formyl-4-(2-fluoro-4-chlorobenzyl)piperazine;
1-formyl-4-(2-methoxy-5-nitrobenzyl)piperazine;
1-formyl-4-(4-methyl-3-nitrobenzyl)piperazine;
1-formyl-4-benzylhomopiperazine;
1-formyl-4-(2-, 3- or 4-chlorobenzyl)-homopiperazine;
1-formyl-4-(2-, 3- or 4-fluorobenzyl)-homopiperazine;
1-formyl-4-(2-, 3- or 4-methylbenzyl)-homopiperazine;
1-formyl-4-(2-, 3- or 4-methoxybenzyl)-homopiperazine;
1-formyl-4-(2-, 3- or 4-trifluoromethyl-benzyl)homopiperazine.

1-Formylpiperazine is commercially available, 1-formylhomopiperazine can be prepared according to the method described in Acta Pharm. Suedica, 7, 7-22 (1970).

Benzylhalides of the formula V are commercially available or can be prepared as described in Bull. Soc. Chim. France, 1959, 349-52.

The compounds of the formula IV can be prepared by any of the methods described in the preparation of the compounds of the formula

II using substituted phenylhalides instead of benzylhalides or from 1-benzyl-4--(substituted phenyl)piperazines or -homopiperazines through the removal of the benzyl group by catalytical hydrogenation. 1-Benzyl-4-(substituted phenyl)piperazines or -homopiperazines are prepared by the reaction of 1-benzylpiperazine or -homopiperazine with a substituted phenylhalide.

The compounds of the formula I have strong influence on both the central and the peripheral serotonergic system. The compounds demonstrate strong affinity to central 5-HT_{2C} receptors, and inhibit the serotonin-evoked contractions of rat stomach fundus smooth muscle strips, moreover, have strong affinity to the central σ_1 ($sigma_1$) receptors, and also inhibit the development of gastric ulcer.

Studies on 5-HT_{2C} receptor binding

5-HT_{2C} receptor binding was measured according to the method of Pazos et al. /Eur. J. Pharmacol., 106, 539 (1985)/. 5-HT_{2C} receptor binding was determined in pig brain choroid plexus membrane preparation using tritiated mesulergine /N'-/(8)-1,6-dimethylergoline-8-il/-N,N-dimetil-sulfonamide/ (70-85 Ci/mmole) as the ligand. Non-specific binding to 5-HT_{2C} receptors was determined in the presence of 1 micromole of mianserin

/1,2,3,4,10,14b-hexahydro-2-methyldibenzo/c,f/-pirazino/1,2-a/azepine/. The final incubation volume was 1 ml. The samples were incubated for 30 minutes at 37 ^{o}C. The incubation was stopped by adding 9 ml of ice-cold 50 mM tris(hydroxymethyl)-aminomethane hydrochloride buffer (pH = 7.7) to the reaction mixture. The samples were rapidly filtered under reduced pressure using Whatman GF/B fiber-glass filters that were soaked in 0.05 % poly(ethylene imine) solution for 2 to 3 hours before use. The radioactivity of the filter disks was determined by liquid scintillation spectroscopy.

The results obtained are shown in Table I.

Table I

The effect of the compounds examined on 5-HT_{2C} receptors

Compound (Example No.)	Inhibition of 5-HT_{2C} receptor binding of the radioactive ligand K_i in nmole/liter
21	48.0
30	59.0

From Table I it can be seen that the compounds of the formula I have considerable affinity for the central nervous system 5-HT_{2C} receptors.

Inhibition of serotonin induced contractions of rat stomach fundus smooth muscle preparations

(The chemical name of serotonin is 3-(2-aminoethyl)-1H-indol-5-ol.)

The tests were performed on male Wistar rats weighing 350 to 400 g. The animals were fasted for 48 hours before the tests, but were allowed to drink tap water ad libitum. The method used was a modified version of that described by Vane et al. /J. Pharmac. Chemother., 12, 344 (1957)/. Rats were killed by decapitation, and their stomachs were removed and in parallel with the great curvature of the stomach 3 mm wide and 20 to 30 mm long strips were cut. The strips were incubated at 37 ^{o}C for 60 minutes in organ chambers of 6 ml capacity. The organ chambers were filled with Tyrode solution (136.9 mM of NaCl, 2.7 mM of KCl, 1.8 mM of $CaCl_2$, 1.0 mM of $MgCl_2$, 11.9 mM of $NaHCO_3$, 5.6 mM of glucose, 0.4 mM of NaH_2PO_4) and was bubbled with a mixture of 5 % of carbon dioxide and 95 % of oxygen. The strips were stretched with 0.5 g during the 60 minutes

equilibration time, and were washed every 20 minutes. The tension was determined isometrically by a K 30 type strain gauge (Hugo Sachs) and recorded by a Graphtech Mark VII 3101 polygraph.

The experimental protocol was as follows:

-Three control contractions were evoked by 5-HT added to the bath in 10^{-7} M concentration (C1, C2, C3).

- If peak C2 and C3 tensions did not differ by more than 10 %, a threshold concentration of the test compounds was added to the bath and the strip was contracted by 5-HT (10^{-7} M) in its presence (T1).

- The effects of the test compounds were determined in five increasing concentrations (T2, T3, T4, T5, T6). Having examined the effect of two concentrations of the test compounds, the control 5-HT response was checked after each test determination.

Data evaluation

IC_{50} was calculated by nonlinear fitting of the inhibitory effect of increasing concentrations of the test compound.

Results:

The compounds of the invention inhibited the 5-HT-evoked contractions of isolated rat stomach fundus smooth muscle strips. The

results obtained are shown in Table II.

Table II

Inhibition of 5-HT-evoked contractions of isolated rat stomach fundus smooth muscle strips

Compound (Example No.)	Inhibition, IC_{50} in nM
21	3.3
22	18.0
24	16.0
25	14.0
26	3.1
27	10.0
28	6.5
29	12.0
30	3.7
47	440.0
51	99.0
52	36.0

Sigma$_1$ (σ_1) receptor binding studies

The σ_1 receptor binding was determined according to the method of Costa et al. /FEBS Lett., 251, 53 (1989)/ with slight modifications. The determination was performed in rat brain cerebellar membrane preparation using tritiated (+)-pentazocine

/2alpha,6alpha,11R)-1,2,3,4,5,6-hexahydro-6,11--dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3--benzazocine-8-ol/ (30-60 Ci/mmole as the ligand). Non-specific binding was determined in the presence of 10 micromole of $(^{+})$-pentazocine. The samples were incubated for 120 minutes at 25 ^{o}C in a final incubation volume of 500 microliter. The incubation was stopped by the addition of 9 ml of ice-cold 10 mM tris(hydroxymethyl)aminomethane hydrochloride puffer (pH=8.0) to the reaction mixture and rapid filtration using reduced pressure. The filtration was performed through Whatman GF/B fiber-glass filters soaked in 0.5 % poly(ethylene imine) solution for 2 to 3 hours before use. The radioactivity of the filter disks was determined by liquid scintillation spectroscopy.

The results obtained are shown in Table III.

Table III
Effect on σ_1 receptors

Compound (Example No.)	Inhibition of σ_1 receptor binding of the radioactive ligand, K_i in nanomole/liter
21	6.0
22	60.0
24	9.0
26	26.0
34	1.6
35	27.0
39	15.0
43	0.8

The determination of the antiulcer effect

Mucosal erosion induced with a mixture of hydrochloric acid and ethanol

The tests were performed on male Wistar rats weighing 180 to 200 g according to the method of Robert et al. /Gastroenterology, 77, 433 (1979)/. The animals were fasted for 24 hours before the experiment, but until 2 hours before the experiment they were allowed to drink tap water ad libitum. Gastric mucosal lesions were induced with a mixture of

hydrochloric acid and ethanol administered orally in a dose of 1 ml/rat. The proportion of hydrochloric acid and ethanol in the mixture (1 volume of 36 per cent aqueous hydrochloric acid and 50 volumes of 99.8 per cent ethanol) was the same as used by Yamazaki et al. /Japan J. Pharmacol., 55, 415 (1991)/. One hour later, the animals were killed with an overdose of ether, the stomachs were removed, and the mucosa was examined with a stereomicroscope at 10 times magnification. The length of each lesion was measured, and the length of lesions were summed up for each stomach. Erosion index was the average lesion length determined in the stomachs of a group of animals. The erosion frequency (i.e. the average number of lesions of animals having at least one erosion) was also estimated. The antiulcer effectiveness of the compounds tested was expressed as the percentage of inhibition of erosion index and the erosion frequency compared to the vehicle (control) group. ED_{50} for erosion index and erosion frequency was calculated using linear regression and Litchfield-Wilcoxon test, respectively. The test compounds were administered orally in 5 ml/kg volume 60 minutes prior to the induction of the gastric mucosal erosion.

Reference compounds used were cetraxate /3-(4-trans-4-aminomethyl-cyclohexylcarbonyl-oxyphenyl)propionic acid/ and sucralfate /the basic aluminium salt of saccharose hydrogen

sulfate/.

The results obtained are shown in Table IV.

Table IV

Compound (Example No.)	ED_{50} in mg/kg, p.o. Inhibition of erosion frequency	erosion index (mm)
21	>30	5.9
22	14.7	4.1
24	10.0	2.1
26	30.5	7.3
30	30.0	3.7
35	>30	8.1
43	50.3	11.4
cetraxate	189.0	22.0
sucralfate	>800	800

Stress-induced ulcus test

The test was performed on male Wistar rats weighing 190 to 210 g and fasted for 24 hours. The test compounds were administered orally in 1 ml/100 g volume with a 30 minutes' pretreatment time. Each treatment group consisted of 8 animals.

Stressing situation was produced by the

method of Takagi and Okabe /Japan J. Pharmacol., 18, 9 (1968)/. The animals were immobilized by placing them into a close metal-wire cage, and for 7 hours they were immersed into a water basin at 23±1 °C to the level of their processus xyphoideus. The animals were removed from the cage and killed with an overdose of ether. The stomachs were removed and fixed for 20 minutes in a 2 % aqueous formaldehyde solution.

The gastric mucosa was examined with a stereomicroscope at 10 times magnification. The length of each lesion was measured and the length of lesions were summed up for each stomachs. The ulcer index is the average lesion length determined in a group of animals. The antiulcer effectiveness of the compounds examined was expressed as the percentage of inhibition of the ulcer index compared to the vehicle (control) group. ED_{50} was calculated using linear regression.

Reference compounds used were ritanserin /6-{2-[4-bis(4-fluorophenyl)methylene]-1-piperidinylethyl}-7-methyl-5H-thiazolo/3,2-a/-pyrimidine-5-one/ and ketanserin /3-{2-[4--(4-fluorobenzoyl)-1-piperidinyl]ethyl}--2,4-(1H,3H)quinazoline-dione/.

The results obtained are shown in Table V.

Table V

Compound (Example No.)	Inhibition of ulcer index (mm) ED_{50} in mg/kg, p.o.
21	0.5
22	4.8
24	8.9
27	2.8
28	1.4
30	6.3
35	3.6
39	3.7
43	4.5
ritanserin	3.6
ketanserin	4.4

Based on the results presented in Tables I to V, the novel compounds of the invention can be used primarily for the treatment of different disorders of the central nervous system. The compounds of the formula I inhibit the serotonin-evoked smooth muscle contractions of rat stomach fundus preparations, and some of the novel compounds are bound to the cerebral 5-HT_{2C} receptors. Data in the scientific literature demonstrate that drugs used for the prophylactic treatment of migraine demonstrate considerable affinity for serotonergic receptors which occurred in the

rat stomach fundus (these receptors are probably the 5-HT_{2B} subtype). The affinity for 5-HT_{2B} receptors was in negative linear correlation with the daily dose of drugs used for the prophylactic treatment of migraine /Kalkman, Life Sci., 54, 641 (1994)/. It has been suggested that 5-HT_{2B} receptor antagonists can have anxiolytic effect as well /Kennett et al., Psychopharmacol., 118, 178 (1995)/.

According to scientific research, the central 5-HT_{2C} receptors play a basic role in the pathomechanism of anxiety disorders, depression, and migraine. The 5-HT_{2C} receptor agonist m-chlorophenylpiperazine /Conn et al., Proc. Natl. Acad. Sci. USA, 83, 4086 (1986)/ induces anxiety both in rats /Kennett et al., Eur. J. Pharmacol., 164, 445 (1989)/ and human beings /Kahn and Weltzer, Biol. Psychiat., 30, 1139 (1991)/. Based on studies performed in rats, the anxiogenic effect of m-chlorophenylpiperazine can be attributed to the activation of the 5-HT_{2C} (formerly 5-HT_{1C}) receptors /Kennett et al., Eur. J. Pharmacol., 164, 445 (1989)/. Compounds with antagonistic effect at 5-$HT_{2A/2C}$ receptors have been shown to be anxiolytic in animal experiments /Kennett., Psychopharmacol., 107, 379 (1992)/. The 5-$HT_{2A/2C}$ receptor antagonistic compound ritanserin proved to be effective for the treatment of different forms of human anxiety /Ceulemans et al., Pharmacopsychiat., 18, 303, (1985)/.

Laboratory investigations demonstrated that most effective antidepressant drugs bind with high affinity to 5-HT_{2C} receptors /Jenck et al., Eur. J. Pharmacol., 231, 223 (1993)/. Based on the above results, it has been suggested that affinity to 5-HT_{2C} receptors might play a role in the therapeutic effectiveness of these compounds.

Usefulness of the compounds of the invention for the treatment of migraine is supported by both the 5-HT_{2C} receptor affinity of the compounds /Sleight et al. in Serotonin Receptor Subtypes: Basic and Clinical Aspects, ed. Peroutka, S.J., pp. 211, Wiley-Liss Inc., (1991)/ and also their activity (Table II) exhibited in the rat stomach fundus test /Kalkman, Life Sci., 54, 641 (1994)/.

A role of serotonergic receptors is assumed in the regulation of food consumption and body temperature, in the development of depression, addiction to drugs and alcohol, some other gastroenterologic and circulatory disorders, and in the pathomechanism of pain /Sleight et al. in Serotonin Receptor Subtypes: Basic and Clinical Aspects, ed. Peroutka, S.J., pp. 211, Wiley-Liss Inc., (1991); Kennett, Drugs, 125 (1995)/.

Strong affinity to $sigma_1$ suggests that the compounds of the invention can be effective in the treatment of disorders of the central nervous system. Several among those compounds bound to $sigma_1$ receptors proved to be

effective antipsychotic agents both in animal experiments and human studies /Ferris et al., J. Pharm. Pharmacol., 32, 388 (1982); Taylor et al., Abstracts Soc. Neurosci., 11, 1304 (1985)/. Antidepressive treatment with compounds having affinity to $sigma_1$ receptors can be another possible therapeutic use /Itzahk and Stein, Life Sci., 47, 1073 (1990)/.

In addition to the above mentioned effects, the compounds of the formula I have strong antiulcer activity. As shown in Tables IV and V, the development and frequency of ulcer are highly inhibited by the novel compounds of the invention in both animal models of ulcer.

Due to the above test results, the novel compounds of the formula I or pharmaceutically acceptable acid addition salts thereof can be used as active ingredients of pharmaceutical compositions. The pharmaceutical compositions of the invention contain a therapeutically active amount of the compound of the formula I or a pharmaceutically acceptable acid addition salt thereof and one or more conventional carrier(s).

The pharmaceutical compositions of the invention are suitable for peroral, parenteral or rectal administration or for local treatment, and can be solid or liquid. In the first place, the compositions are useful for the treatment of a disease of the central nervous system and/or gastric ulcer.

Especially, the pharmaceutical compositions of the invention may be used for the treatment of anxiety and/or migraine.

The solid pharmaceutical compositions suitable for peroral administration may be powders, capsules, tablets, film-coated tablets, microcapsules etc., and can comprise binding agents such as gelatine, sorbitol, poly(vinylpyrrolidone) etc.; filling agents such as lactose, glucose, starch, calcium phosphate etc.; auxiliary substances for tabletting such as magnesium stearate, talc, poly(ethyleneglycol), silica etc.; wetting agents such as sodium laurylsulfate etc. as the carrier.

The liquid pharmaceutical compositions suitable for peroral administration may be solutions, suspensions or emulsions and can comprise e.g. suspending agents such as gelatine, carboxymethylcellulose etc.; emulsifiers such as sorbitane monooleate etc.; solvents such as water, oils, glycerol, propyleneglycol, ethanol etc.; preservatives such as methyl p-hydroxybenzoate etc. as the carrier.

Pharmaceutical compositions suitable for parenteral administration consist of sterile solutions of the active ingredient, in general.

Dosage forms listed above as well as other dosage forms are known per se, see e.g. Remington's Pharmaceutical Sciences, 18th

Edition, Mack Publishing Co., Easton, USA (1990).

The pharmaceutical compositions of the invention contain, in general, 0.1 to 95.0 per cent by mass of a compound of the formula I or a pharmaceutically acceptable acid addition salt thereof. A typical dose for adult patients amounts to 0.1 to 20 mg of the compound of the formula I or a pharmaceutically acceptable acid addition salt thereof, daily. The above dose can be administered in one or more portions. The actual dosage depends on many factors and is determined by the doctor.

The pharmaceutical compositions of the invention are prepared by admixing a compound of the formula I or a pharmaceutically acceptable acid addition salt thereof to one or more carrier(s), and converting the mixture obtained to a pharmaceutical composition in a manner known per se. Useful methods are known from the literature, e.g. Remington's Pharmaceutical Sciences.

Suitably, the pharmaceutical compositions of the invention contain a piperazine derivative of the formula I, wherein

R^1 stands for a chloro, a fluoro, a methyl group, a methoxy group, a nitro group or a trifluoromethyl group,

m is 0, 1 or 2,

R^2, R^3 and R^4 represent, independently, a hydrogen, a chloro, a methyl group, a

methoxy group, a trifluoromethyl group, a nitro group, an amino group, a formyl group or a carboxy group,

n is 1 or 2,

or a pharmaceutically acceptable acid addition salt thereof as the active ingredient.

Preferably, the pharmaceutical compositions of the invention contain a piperazine derivative of the formula I, wherein

R^1 stands for a chloro, a fluoro, a methyl group or a methoxy group,

m is 0 or 1,

R^2, R^3 and R^4 represent, independently, a hydrogen, a chloro, a methyl group, a methoxy group, a trifluoromethyl group, a nitro group, an amino group or a formyl group,

n is 1,

or a pharmaceutically acceptable acid addition salt thereof as the active ingredient.

The invention includes a medical treatment process, too. According to this use, a patient suffering especially in a disease of the central nervous system or in gastric ulcer is treated with a therapeutically active, non-toxic quantity of a piperazine derivative of the formula I or a pharmaceutically acceptable acid addition salt thereof. The disease of the central nervous system is, especially, migraine, anxiety or depression.

The invention is further elucidated by means of the following Examples:

General method of preparation of the compounds of the formula VI:

To a solution of 0.5 moles of 1-formylpiperazine or 1-formylhomopiperazine in 300 cm^3 of ethanol, 69 g (0.5 moles) of potassium carbonate are added. To the mixture stirred at room temperature for 30 minutes, 0.5 moles of a compound of the formula V are added, drop by drop. The reaction mixture is kept at the temperature specified in the Examples for the time given in the Examples, then the inorganic salts are removed by filtration, and the filtrate is evaporated. The residue consisting of an oil and some inorganic salts is treated with acetone, the salts are separated by filtration, and the organic solution is evaporated.

The following compounds of the formula VI have been prepared using the above method:

Example 1

1-Formyl-4-(2-chlorobenzyl)piperazine

Reaction temperature: 80 °C.
Reaction time: 2 hours.
Yield: 105.45 g (88.3 %).
Analysis for $C_{12}H_{15}ClN_2O$ (238.715)
calculated: C 60.38%, H 6.33%, Cl 14.85%, N 11.73%;
found: C 59.78%, H 6.21%, Cl 15.25%, N 11.53%;

Example 2

1-Formyl-4-(3-chlorobenzyl)piperazine

Reaction temperature: room temperature.
Reaction time: 4.5 hours.
Yield: 118 g (98.9 %).
Analysis for $C_{12}H_{15}ClN_2O$ (238.715)
calculated: C 60.38%, H 6.33%, Cl 14.85%,
N 11.73%;
found: C 58.75%, H 6.18%, Cl 15.02%,
N 11.51%.
^{1}H-NMR (200 MHz, $CDCl_3$) ppm:
8.01 (1H, s), 7.34 (1H, s), 7.16-7.28 (3H, m), 3.52-3.58 (2H, m), 3.50 (2H, s), 3.34-3.42 (2H, m), 2.382.46 (4H, m).

Example 3

1-Formyl-4-(4-chlorobenzyl)piperazine

Reaction temperature: 80 °C.
Reaction time: 1.5 hours.
Yield: 115.54 g (96.8 %).
Analysis for $C_{12}H_{15}ClN_2O$ (238.715)
calculated: C 60.38%, H 6.33%, Cl 14.85%,
N 11.73%;
found: C 59.22%, H 6.26%, Cl 15.48%,
N 11.24%.

Example 4

1-Formyl-4-(3-trifluoromethylbenzyl)piperazine

Reaction temperature: 80 °C.

Reaction time: 3 hours.
Yield: 132.4 g (97.0 %).
Analysis for $C_{13}H_{15}F_3N_2O$ (272.273)
calculated: C 57.35%, H 5.55%, N 10.29%;
found: C 57.12%, H 5.38%, N 10.15%.

Example 5
1-Formyl-4-(2-methylbenzyl)piperazine

Reaction temperature: 50 °C.
Reaction time: 4.5 hours.
Yield: 97.25 g (89.1 %).
Analysis for $C_{13}H_{18}N_2O$ (218.301)
calculated: C 71.53%, H 8.31%, N 12.83%;
found: C 70.89%, H 8.12%, N 12.75%.

Example 6
1-Formyl-4-(4-methylbenzyl)piperazine

Reaction temperature: 50 °C.
Reaction time: 4.5 hours.
Yield: 104.0 g (95.2 %).
Analysis for $C_{13}H_{18}N_2O$ (218.301)
calculated: C 71.53%, H 8.31%, N 12.83%;
found: C 71.18%, H 8.28%, N 12.67%.
^{1}H-NMR (200 MHz, $CDCl_3$) ppm:
7.99 (1H, s), 7.08-7.22 (4H, m), 3.50-3.58 (2H, m), 3.48 (2H, s), 3.30-3.38 (2H, m), 2.35-2.45 (4H, m), 2.33 (3H, s).

Example 7
1-Formyl-4-(2-fluorobenzyl)piperazine

Reaction temperature: 80 °C.
Reaction time: 22 hours.
Yield: 108.35 g (97.6 %).
Analysis for $C_{12}H_{15}FN_2O$ (222.265)
calculated: C 64.85%, H 6.80%, N 12.60%;
found: C 65.17%, H 6.49%, N 12.53%.
^{1}H-NMR (200 MHz, $CDCl_3$) ppm:
8.00 (1H, s), 6.98-7.42 (4H, m), 3.61 (2H, s, J_{HF} 1.3 Hz), 3.52-3.59 (2H, m), 3.34-3.41 (2H, m), 2.42-2.52 (4H, m).

Example 8

1-Formyl-4-(3-fluorobenzyl)piperazine

Reaction temperature: 80 °C.
Reaction time: 25 hours.
Yield: 111.95 g (100 %).
Analysis for $C_{12}H_{15}FN_2O$ (222.265)
calculated: C 64.85%, H 6.80%, N 12.60%;
found: C 64.72%, H 6.51%, N 12.49%.

Example 9

1-Formyl-4-(4-fluorobenzyl)piperazine

Reaction temperature: 80 °C.
Reaction time: 22 hours.
Yield: 111.95 g (100 %).
Analysis for $C_{12}H_{15}FN_2O$ (222.265)
calculated: C 64.85%, H 6.80%, N 12.60%;
found: C 65.13%, H 6.75%, N 12.49%.

Example 10

1-Formyl-4-(2,6-dichlorobenzyl)piperazine

Reaction temperature: room temperature.
Reaction time: 15 hours.
Yield: 113 g (82.7 %).
Analysis for $C_{12}H_{14}Cl_2N_2O$ (273.168)
calculated: C 52.76%, H 5.17%, Cl 25.96%,
N 10.25%;
found: C 50.98%, H 5.08%, Cl 25.73%,
N 9.98%.

Example 11

1-Formyl-4-(2-fluoro-6-chlorobenzyl)piperazine

Reaction temperature: room temperature.
Reaction time: 9 hours.
Yield: 110.55 g (86.1 %).
Analysis for $C_{12}H_{14}ClFN_2O$ (256.708)
calculated: C 56.15%, H 5.50%, Cl 13.81%,
N 10.91%;
found: C 54.83%, H 5.38%, Cl 13.65%,
N 10.87%.

Example 12

1-Formyl-4-(4-methyl-3-nitrobenzyl)piperazine

Reaction temperature: room temperature.
Reaction time: 25 hours.
Yield: 99 g (75.2 %).
Analysis for $C_{13}H_{17}N_3O_3$ (263.298)
calculated: C 59.30%, H 6.51%, N 15.96%;

found: C 58.15%, H 6.18%, N 15.73%.

Example 13

1-Formyl-4-benzylhomopiperazine

Reaction temperature: room temperature.
Reaction time: 14.5 hours.
Yield: 102.43 g (93.8 %).
Analysis for $C_{13}H_{18}N_2O$ (218.300)
calculated: C 71.53%, H 8.31%, N 12.83%;
found: C 69.18%, H 8.25%, N 12.62%.

Example 14

1-Formyl-4-(3-methoxybenzyl)homopiperazine

Reaction temperature: 80 ^{o}C.
Reaction time: 12 hours.
Yield: 107.0 g (92.3 %).
Analysis for $C_{14}H_{20}N_2O_2$ (248.327)
calculated: C 67.72%, H 8.12%, N 11.28%;
found: C 65.78%, H 8.03%, N 10.96%.

Example 15

1-Formyl-4-(4-methoxybenzyl)homopiperazine

Reaction temperature: room temperature.
Reaction time: 11.5 hours.
Yield: 121.2 g (97.6 %).
Analysis for $C_{14}H_{20}N_2O_2$ (248.327)
calculated: C 67.72%, H 8.12%, N 11.28%;
found: C 66.17%, H 8.10%, N 11.13%.

Example 16

1-Formyl-4-(2-chlorobenzyl)homopiperazine

Reaction temperature: room temperature.
Reaction time: 14 hours.
Yield: 125.75 g (99.5 %).
Analysis for $C_{13}H_{17}ClN_2O$ (252.742)
calculated: C 61.78%, H 6.78%, Cl 14.03%,
N 11.08%;
found: C 60.17%, H 6.63%, Cl 13.87%,
N 10.96%.

Example 17

1-Formyl-4-(3-chlorobenzyl)homopiperazine

Reaction temperature: room temperature.
Reaction time: 12 hours.
Yield: 125 g (98.9 %).
Analysis for $C_{13}H_{17}ClN_2O$ (252.742)
calculated: C 61.78%, H 6.78%, Cl 14.03%,
N 11.08%;
found: C 60.95%, H 6.43%, Cl 13.95%,
N 11.15%.

Example 18

1-Formyl-4-(2-fluorobenzyl)homopiperazine
Reaction temperature: room temperature.
Reaction time: 14 hours.
Yield: 114.0 g (96.5 %).
Analysis for $C_{13}H_{17}FN_2O$ (236.297)
calculated: C 66.08%, H 7.25%, N 11.85%;
found: C 64.78%, H 7.12%, N 11.73%.

Example 19

1-Formyl-4-(3-fluorobenzyl)homopiperazine

Reaction temperature: room temperature.
Reaction time: 12 hours.
Yield: 113.0 g (95.6 %).
Analysis for $C_{13}H_{17}FN_2O$ (236.297)
calculated: C 66.08%, H 7.25%, N 11.85%;
found: C 63.58%, H 7.05%, N 11.59%.

Example 20

1-Formyl-4-(4-fluorobenzyl)homopiperazine

Reaction temperature: room temperature.
Reaction time: 7 hours.
Yield: 118.04 g (99.9 %).
Analysis for $C_{13}H_{17}FN_2O$ (236.297)
calculated: C 66.08%, H 7.25%, N 11.85%;
found: C 66.32%, H 7.18%, N 11.63%.

Preparation of the compounds of the formula I

Example 21

1-Benzyl-4-(5-amino-4-methyl-2-nitrophenyl)-piperazine hydrochloride

Method a)

To a solution of 7.06 g (0.04 moles) of 1-benzylpiperazine in 100 cm^3 of ethanol, 11.04 g (0.08 moles) of potassium carbonate,

then 13.06 g (0.04 moles) of 5-chloro--2-methyl-4-nitroaniline are added, and the reaction mixture is boiled for 40 hours. The suspension is filtered to remove the inorganic salts, and the filtrate is evaporated. The oil obtained is purified by column chromatography using a mixture of 98 volumes of chloroform and 2 volumes of methanol as the eluant. The fraction containing the product is diluted with isopropanol and reacted with an about tenfold excess of hydrogen chloride in isopropanol to form the hydrochloride salt.

4.9 g (30.7 %) of the title compound are obtained in the form of yellow crystals.
M.p.: 226-227 °C.
Analysis for $C_{18}H_{24}Cl_2N_4O_2$ (399.324)
calculated: C 54.14%, H 6.06%,
Cl(ionic) 17.76%, N 14.03%;
found: C 54.21%, H 6.18%,
Cl(ionic) 17.14%, N 13.65%.

Method b)

11.04 g (0.08 moles) of potassium carbonate are added to a solution of 7.06 g (0.04 moles) of 1-benzylpiperazine in 60 cm^3 of dimethylformamide, and the mixture is stirred at room temperature for 0.5 hours. Then, 7.46 g (0.04 moles) of 5-chloro--2-methyl-4-nitroaniline are added, and the reaction mixture is stirred at 120 °C for

45 hours. After cooling with ice water, the inorganic salts are filtered, and the filtrate is evaporated to obtain an oil that is treated with 40 cm^3 of a mixture consisting of 95 volumes of chloroform and 5 volumes of methanol. A part of the unreacted 5-chloro-2-methyl-4-nitroaniline separates in the form of crystals that are filtered. The filtrate is purified by column chromatography using a mixture of 98 volumes of chloroform and 2 volumes of methanol as the eluant. The pure base is reacted in an isopropanolic medium with about 10 equivalents of hydrogen chloride in isopropanol to obtain the hydrochloride.

12.55 g (78.6 %) of the title compound are obtained in the form of yellow crystals.
M.p.: 227-229 °C.
Analysis for $C_{18}H_{24}Cl_2N_4O_2$ (399.324)
calculated: C 54.14%, H 6.06%,
Cl(ionic) 17.76%, N 14.03%;
found: C 53.91%, H 6.15%,
Cl(ionic) 17.33%, N 14.25%.

Example 22
1-(2-Chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride

5.67 g (0.02 moles) of 1-(4-chlorobenzyl)piperazine dihydrochloride and 3.73 g (0.02 moles) of 5-chloro-2--methyl-4-nitroaniline are reacted in the

presence of 5.52 g (0.04 moles) of potassium carbonate for 60 hours according to method b) of Example 21. The crude product obtained is purified by flash chromatography using a mixture of 93 volumes of chloroform and 7 volumes of methanol as the eluent, then the dihydrochloride salt is formed by the method described in Example 21.

5.58 g (64.3 %) of the title compound are obtained as yellow solids. M.p.: 217-218 ^{o}C.

Analysis for $C_{18}H_{23}Cl_3N_4O_2$ (433.769)

calculated: C 49.84%, H 5.34%,
Cl(total) 24.52%,
Cl(ionic) 16.35%, N 12.92%;

found: C 48.94%, H 5.58%,
Cl(total) 23.83%,
Cl(ionic) 15.76%, N 13.01%.

Example 23

1-(3-Chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride

8.50 g (0.03 moles) of 1-(3-chlorobenzyl)piperazine dihydrochloride and 5.6 g (0.03 moles) of 5-chloro-2-methyl-4--nitroaniline are reacted in the presence of 8.28 g (0.06 moles) of potassium carbonate and 0.5 g (0.03 moles) of potassium iodide for 36 hours according to method b) of Example 21. The base obtained is purified by column chromatography using a mixture of 93 volumes

of chloroform and 7 volumes of methanol as the eluent. Then, the dihydrochloride salt is formed by the method described in Example 21.

4.3 g (33 %) of the title compound are obtained as yellow solids. M.p.: 215-217 °C.
Analysis for $C_{18}H_{23}Cl_3N_4O_2$ (433.769)
calculated: C 49.84%, H 5.34%,
Cl(total) 24.52%,
Cl(ionic) 16.35%, N 12.92%;
found: C 49.10%, H 5.29%,
Cl(total) 24.28%,
Cl(ionic) 16.27%, N 12.50%.

Example 24
1-(4-Chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride

5.67 g (0.02 moles) of 1-(4-chlorobenzyl)-piperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro-2-methyl--4-nitroaniline in the presence of 5.52 g (0.04 moles) of potassium carbonate according to method b) of Example 21 (the reaction mixture is boiled for 30 hours). The crude base obtained is purified by flash chromatography using a mixture of 97 volumes of chloroform and 3 volumes of methanol as the eluent. Then, the dihydrochloride salt is formed as described in Example 21, method b).

4.47 g (51.5 %) of the title compound

are obtained as yellow solids.
M.p.: 191-193 °C.
Analysis for $C_{18}H_{23}Cl_3N_4O_2$ (433.769)
calculated: C 49.84%, H 5.34%,
Cl(total) 24.52%,
Cl(ionic) 16.35%, N 12.92%;
found: C 48.03%, H 5.51%,
Cl(total) 23.95%,
Cl(ionic) 15.76%, N 12.44%.

Example 25

1-(2-Fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride

5.34 g (0.02 moles) of 1-(2-fluorobenzyl)piperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro-2--methyl-4-nitroaniline in the presence of 5.52 g (0.02 moles) of potassium carbonate and 0.3 g (0.002 moles) of potassium iodide for 33 hours according to method b) of Example 21. The residue is purified by flash chromatography using a mixture of 97 volumes of chloroform and 3 volumes of methanol as the eluent. Then, the pure base is reacted in ethanolic solution with about 10 equivalents of hydrogen chloride in ethanol to obtain the dihydrochloride salt.

6.92 g (83 %) of the title compound are obtained as yellow solids. M.p.: 222 °C.
Analysis for $C_{18}H_{23}Cl_2FN_4O_2$ (417.314)

calculated: C 51.81%, H 5.56%,
Cl(ionic) 16.99%, N 13.34%;
found: C 51.43%, H 5.70%,
Cl(ionic) 16.93%, N 13.72%.

Example 26

1-(3-Fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride

5.34 g (0.02 moles) of 1-(3-fluorobenzyl)-piperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro-2-methyl--4-nitroaniline for 44 hours according to the method described in Example 25.

4.27 g (51.2 %) of the title compound are obtained as yellow solids. M.p.: 223 ^{o}C.
Analysis for $C_{18}H_{23}Cl_2FN_4O_2$ (417.314)
calculated: C 51.81%, H 5.56%,
Cl(ionic) 16.99%, N 13.34%;
found: C 51.54%, H 5.63%,
Cl(ionic) 16.73%, N 13.34%.

Example 27

1-(4-Fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride

5.34 g (0.02 moles) of 1-(4-fluorobenzyl)-piperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro-2-methyl--4-nitroaniline according to the method described in Example 25. After a purification by flash chromatography using a mixture of

95 volumes of chloroform and 5 volumes of methanol as the eluent, 6.48 g (77.6 %) of the title compound are obtained. M.p.: 226 °C.

Analysis for $C_{18}H_{23}Cl_2FN_4O_2$ (417.314)
calculated: C 51.81%, H 5.56%,
Cl(ionic) 16.99%, N 13.34%;
found: C 51.47%, H 5.75%,
Cl(ionic) 16.44%, N 13.80%.

Example 28

1-(2-Methylbenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine hydrochloride

5.27 g (0.02 moles) of 1-(2-methylbenzyl)-piperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro-2-methyl--4-nitroaniline for 18 hours according to the method of Example 27. 5.51 g (73.1 %) of the title compound are obtained as orange yellow crystals. M.p.: 272 °C.

Analysis for $C_{19}H_{25}ClN_4O_2$ (376.890)
calculated: C 60.55%, H 6.69%, Cl(ionic) 9.41%,
N 14.87%;
found: C 60.85%, H 6.70%, Cl(ionic) 9.66%,
N 14.59%.

Example 29

1-(4-Methylbenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine hydrochloride

Method a)

5.27 g (0.02 moles) of 1-(4-methylbenzyl)-piperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro-2-methyl-4-nitroaniline for 40 hours according to the method of Example 25. After a purification by flash chromatography using a mixture of 93 volumes of chloroform and 7 volumes of methanol as the eluent, 3.5 g (46.4 %) of the title compound are obtained as yellow solids. M.p.: 198-200 °C.

Analysis for $C_{19}H_{25}ClN_4O_2$ (376.890)

calculated: C 60.55%, H 6.69%, Cl(ionic) 9.41%, N 14.87%;

found: C 57.77%, H 6.75%, Cl(ionic) 9.32%, N 14.32%.

Method b)

A mixture of 2.63 g (0.01 moles) of 1-(4-methylbenzyl)piperazine dihydrochloride, 1,38 g (0.01 moles) of potassium carbonate and 50 cm^3 of water is stirred for 30 minutes, then 1.87 g (0.01 moles) of 5-chloro-2-methyl--4-nitroaniline are added, the reaction mixture is boiled for 40 hours, and filtered while hot. The crystals separated are dried, recrystallized from ethanol, and the pure base dissolved in ethanol is reacted with hydrogen chloride in ethanol to form the hydrochloride salt.

2.83 g (75.1 %) of the title compound are obtained as yellow solids.
M.p.: 199-200 °C.
Analysis for $C_{19}H_{25}ClN_4O_2$ (376.890)
calculated: C 60.55%, H 6.69%, Cl(ionic) 9.41%, N 14.87%;
found: C 58.97%, H 6.73%, Cl(ionic) 9.35%, N 14.43%.

Example 30
1-(3-Methoxybenzyl)-4-(5-amino-4-methyl-2--nitrophenyl)piperazine dihydrochloride

13.8 g (0.05 moles) of 1-(3-methoxybenzyl)piperazine dihydrochloride are reacted with 9.3 g (0.05 moles) of 5-chloro-2--methyl-4-nitroaniline in the presence of 13.8 g (0.1 moles) of potassium carbonate for 60 hours at reflux temperature according to method b) of Example 21. The eluent consists of 93 volumes of chloroform and 7 volumes of methanol. 10.23 g (47.6 moles) of the title compound are obtained as yellow solids. M.p.: 216 °C.
Analysis for $C_{19}H_{26}Cl_2N_4O_2$ (429.350)
calculated: C 53.15%, H 6.10%, Cl(ionic) 16.52%, N 13.05%;
found: C 52.98%, H 6.26%, Cl(ionic) 16.77%, N 12.57%.

Example 31

1-Benzyl-4-(2,5-diamino-4-methylphenyl)-piperazine trihydrochloride

7.2 g (0.018 moles) of 1-benzyl-4--(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride are dissolved in 1800 cm^3 of ethanol. The solution obtained is hydrogenized in the presence of 0.6 g of palladium/carbon (Selcat Q) catalyst at 25 ^oC under a pressure of $4x10^5$ Pa. Then the catalyst is removed by filtration, and the filtrate is evaporated. The residue is dissolved in 50 cm^3 of water, the aqueous phase is made alkaline (pH 8) by the addition of potassium carbonate, and extracted with chloroform 4 times using 50 cm^3 of chloroform each time. The organic solutions are evaporated to obtain the crude base that is purified by column chromatography using a mixture of 85 volumes of chloroform and 15 volumes of methanol as the eluent. The pure base dissolved in isopropanol is reacted with hydrogen chloride in isopropanol under ice cooling to obtain the trihydrochloride salt.

5.05 g (69.1 %) of the title compound are obtained as pale drab solids.

M.p.: 274-275 ^oC.

Analysis for $C_{18}H_{27}Cl_3N_4$ (405.802)

calculated: C 53.28%, H 6.71%,

Cl(ionic) 26.21%, N 13.80%;

found: C 51.27%, H 6.47%,
Cl(ionic) 25.31%, N 13.25%.

Example 32
1-(2,6-Dichlorobenzyl)-4-(5-amino-4-methyl-3-nitrophenyl)piperazine hydrochloride

12.76 g (0.04 moles) of 1-(2,6-dichlorobenzyl)piperazine dihydrochloride are reacted with 7.46 g (0.04 moles) of 5-chloro-2-methyl--4-nitroaniline in the presence of 11.04 g (0.08 moles) of potassium carbonate and 0.6 g (0.004 moles) of potassium iodide according to method b) of Example 21. The oily product remaining after the removal of the solvent is treated with acetone, the rest of inorganic salts are filtered, the filtrate is evaporated, and the residual oil is treated with 70 cm^3 of ethanol to obtain the crystals of the base that are dissolved in ethanol and reacted with an about tenfold excess of hydrogen chloride in ethanol to form the hydrochlorid salt.

10.78 g (62.4 %) of the title compound are obtained as light yellow solids. M.p.: 246-248 ^oC.

Analysis for $C_{18}H_{21}Cl_3N_4O_2$ (431.753)
calculated: C 50.08%, H 4.90%,
Cl(total) 24.63%,
Cl(ionic) 8.21%, N 12.98%;
found: C 48.92%, H 4.81%,
Cl(total) 24.20%,

Cl(ionic) 8.33%, N 12.39%.

Example 33

1-(2-Fluoro-6-chlorobenzyl)-4-(5-amino-4--methyl-2-nitrophenyl)piperazine dihydrochloride monohydrate

6.04 g (0.02 moles) of 1-(2-fluoro-6--chlorobenzyl)piperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro--2-methyl-4-nitroaniline in the presence of 5.52 g (0.04 moles) of potassium carbonate and 0.3 g (0.002 moles) of potassium iodide by the method described in Example 32. The oil obtained after the treatment with acetone is dissolved in 80 cm^3 of ethanol and reacted with an about tenfold excess of hydrogen chloride to form the dihydrochloride salt. The crystalline product that forms is filtered and suspended in 20 cm^3 of water.

6.06 g (64.5 %) of the title compound are obtained as yellow crystals.

M.p.: 242-244 °C.

Analysis for $C_{18}H_{24}Cl_3FN_4O_3$ (469.774)

calculated: C 46.02%, H 5.15%,
Cl(total) 22.64%,
Cl(ionic) 15.09%, N 11.93%;

found: C 47.19%, H 5.15%,
Cl(total) 22.70%,
Cl(ionic) 14.96%, N 11.89%.

Example 34

1-Benzyl-4-(4,5-dimethoxy-2-nitrophenyl)-piperazine

2.76 g (0.02 moles) of potassium carbonate are added to 30.51 g (0.17 moles) of 1-benzyl-piperazine, and the mixture is stirred for 30 minutes. To the mixture, 2.16 g (0.01 moles) of 4,5-dimethoxy-2-nitrochlorobenzene are added, and the reaction mixture is stirred at 80 ^{o}C for 16 hours, then cooled to room temperature, and poured onto 140 cm^3 of ice water.

2 g (56 %) of the title compound are obtained as orange solids. M.p.: 98-100 ^{o}C.
Analysis for $C_{19}H_{23}N_3O_4$ (357.413)
calculated: C 63.85%, H 6.49%, N 11.76%;
found: C 63.96%, H 6.58%, N 11.68%.

Example 35

1-(2-Chlorobenzyl)-4-(4,5-dimethoxy-2-nitro-phenyl)piperazine

5.5 g (0.019 moles) of 1-(2-chloro-benzyl)piperazine dihydrochloride are dissolved in 120 cm^3 of dimethylformamide. To the solution obtained, 5.52 g (0.04 moles) of potassium carbonate are added, and the mixture is stirred at room temperature for 30 minutes. Then 0.6 g (0.004 moles) of potassium iodide and 4.22 g (0.019 moles) of 4,5-dimethoxy-chlorobenzene are added, and the reaction

mixture is stirred at 110 °C for 52 hours. The inorganic salts are filtered, the filtrate is poured onto water, the product precipitated is filtered and purified by column chromatography using a mixture of 1 volumes of hexane and 1 volumes of ethyl acetate as the eluent.

2.81 g (37.7 %) of the title compound are obtained as orange solids.

M.p.: 140-143 °C.

Analysis for $C_{19}H_{22}ClN_3O_4$ (391.585)

calculated: C 58.24%, H 5.66%, Cl 9.04%, N 10.72%;

found: C 57.37%, H 5.77%, Cl 8.70%, N 10.39%.

Example 36

1-(3-Chlorobenzyl)-4-(4,5-dimethoxy-2-nitrophenyl)piperazine

7.09 g (0.025 moles) of 1-(3-chlorobenzyl)piperazine dihydrochloride are reacted with 5.44 g (0.025 moles) of 4,5-dimethoxy--2-nitrochlorobenzene for 45 hours according to the method described in Example 35. Purification: recrystallization from isopropanol.

4.88 g (49.8 %) of the title compound are obtained as orange solids. M.p.: 79-81 °C.

Analysis for $C_{19}H_{22}ClN_3O_4$ (391.858)

calculated: C 58.24%, H 5.66%, Cl 9.04%,
N 10.72%;
found: C 58.09%, H 5.85%, Cl 9.21%,
N 10.59%.

Example 37

1-(3-Trifluoromethylbenzyl)-4-(4,5-dimethoxy-2-nitrophenyl)piperazine

Method a)

6.32 g (0.02 moles) of 1-(3-trifluoromethylbenzyl)piperazine dihydrochloride are reacted with 4.35 g (0.02 moles) of 4,5-dimethoxy-2-nitrochlorobenzene for 50 hours according to the method described in Example 35. 5.05 g (59.3 %) of the title compound are obtained as red solids. M.p.: 117-120 °C.

Analysis for $C_{20}H_{22}F_3N_3O_4$ (425.411)
calculated: C 56.47%, H 5.21%, N 9.88%;
found: C 56.86%, H 5.46%, N 9.77%.

Method b)

To the solution of 1.0 g (0.003 moles) of 1-(3-trifluoromethylbenzyl)piperazine dihydrochloride in 50 cm^3 of methyl Cellosolve (2-methoxyethanol), 0.83 g (0.006 moles) of potassium carbonate are added, and the mixture is stirred at room temperature for 30 minutes. Then 0.65 g (0.003 moles) of 4,5-dimethoxy-

-2-nitrochlorobenzene and 0.05 g (0.0003 moles) of potassium iodide are added, and the reaction mixture is stirred at 110 °C for 55 hours. After cooling, the inorganic salts are filtered, the filtrate is evaporated. The residue is purified by column chromatography.

0.82 g (64.5 %) of the title compound are obtained as red solids. M.p.: 117-119 °C.

Analysis for $C_{20}H_{22}F_3N_3O_4$ (425.411)
calculated: C 56.47%, H 5.21%, N 9.88%;
found: C 57.19%, H 5.13%, N 9.69%.

Example 38

1-(3-Fluorobenzyl)-4-(4,5-dimethoxy-2-nitrophenyl)piperazine

8.02 g (0.03 moles) of 1-(3-fluorobenzyl)-piperazine dihydrochloride are reacted with 6.52 g (0.03 moles) of 4,5-dimethoxy--2-nitrochlorobenzene at 100 °C for 50 hours according to the method described in Example 35. 3.97 g (35.2 %) of the title compound are obtained as orange solids.
M.p.: 99-102 °C.
Analysis for $C_{19}H_{22}FN_3O_4$ (375.403)
calculated: C 60.79%, H 5.91%, N 11.19%;
found: C 59.44%, H 5.88%, N 10.83%.

Example 39

1-(2-Fluorobenzyl)-4-(4,5-dimethoxy-2-nitrophenyl)piperazine

6.5 g (0.024 moles) of 1-(2-fluorobenzyl)piperazine dihydrochloride are reacted with 5.29 g (0.024 moles) of 4,5-dimethoxy--2-nitrochlorobenzene at 100 °C for 55 hours according to the method described in Example 35. 5.42 g (60.2 %) of the title compound are obtained. M.p.: 121-123 °C.
Analysis for $C_{19}H_{22}FN_3O_4$ (375.403)
calculated: C 60.79%, H 5.91%, N 11.19%;
found: C 60.10%, H 5.88%, N 11.08%.

Example 40
1-(3-Methoxybenzyl)-4-(4,5-dimethoxy-2-nitrophenyl)piperazine

6.7 g (0.025 moles) of 1-(3-methoxybenzyl)piperazine dihydrochloride are reacted with 5.45 g (0.025 moles) of 4,5-dimethoxy--2-nitrochlorobenzene for 50 hours according to the method described in Example 35. Eluent: a mixture of 96 volumes of toluene and 4 volumes of methanol. 4.23 g (43.7 %) of the title compound are obtained as orange solids. M.p.: 83-85 °C.
Analysis for $C_{20}H_{25}N_3O_5$ (387.439)
calculated: C 62.00%, H 6.50%, N 10.85%;
found: C 61.35%, H 6.73%, N 10.62%.

Example 41
1-(4-Methylbenzyl)-4-(4,5-dimethoxy-2-nitrophenyl)piperazine

A solution of 16.0 g (0.061 moles) of 4-methylbenzylpiperazine dihydrochloride in 300 cm^3 of acetonitrile is stirred with 15.45 g (0.0112 moles) of potassium carbonate at room temperature for 30 minutes, then 13.27 g (0.061 moles) of potassium iodide are added, and the reaction mixture is boiled for 50 hours. The mixture is cooled to room temperature, the inorganic salts are filtered, the filtrate is evaporated, and the residue is purified by column chromatography using a mixture of 1 volume of hexane and 1 volume of ethyl acetate as the eluent.

16.53 g (73.2 %) of the title compound are obtained as yellow solids.
M.p.: 119-123 °C.
Analysis for $C_{20}H_{25}N_3O_4$ (371.44)
calculated: C 64.67%, H 6.78%, N 11.31%;
found: C 63.89%, H 6.57%, N 11.68%.

Example 42
1-(2-Methylbenzyl)-4-(4,5-dimethoxy-2-nitrophenyl)- piperazine

11.09 g (0.042 moles) of 2-methylbenzylpiperazine dihydrochloride are reacted with 9.54 g (0.042 moles) of 4,5-dimethoxy--2-nitrochlorobenzene in the presence of catalytic amount of potassium iodide for 60 hours according to the method described in Example 41. The reaction mixture is poured onto ice water to separate the product that

is purified by column chromatography using a mixture of 1 volume of hexane and 1 volume of ethyl acete as the eluent.

11.09 g (71.1 %) of the title compound are obtained as orange solids.
M.p.: 122-124 °C.
Analysis for $C_{20}H_{25}N_3O_4$ (371.44)
calculated: C 64.67%, H 6.78%, N 11.31%;
found: C 64.08%, H 6.82%, N 11.32%.

Example 43
1-Benzyl-4-(2-amino-4-trifluoromethylphenyl)-piperazine dihydrochloride

2.76 g (0.02 moles) of potassium carbonate are added to a solution of 4.91 g (0.02 moles) of 1-(2-amino-4-trifluoromethylphenyl)-piperazine in 50 cm^3 of ethanol, and the mixture is stirred for 30 minutes. Then 2.6 g (0.02 moles) of benzyl chloride are added, drop by drop, and the reaction mixture is boiled for 5 hours. The inorganic salts are filtered, and the filtrate is evaporated. The residual oil crystallizes on standing. The crystals are suspended in water, filtered, dried, then dissolved in isopropanol and reacted with about tenfold excess of hydrogen chloride in isopropanol to form the dihydrochloride salt.

6.22 g (76.2 %) of the title compound are obtained as light drab solids.
M.p.: 233-234 °C.

Analysis for $C_{18}H_{22}Cl_2F_3N_4$ (408.297)
calculated: C 52.95%, H 5.43%,
Cl(ionic) 17.37%, N 10.29%;
found: C 51.85%, H 5.32%,
Cl(ionic) 17.31%, N 9.98%.

Example 44

1-(2-Chlorobenzyl)-4-(2-amino-4-trifluoromethylphenyl)piperazine hydrochloride hydrate

2.1 g (0.015 moles) of potassium carbonate are added to a solution of 3.68 g (0.015 moles) of 1-(2-amino-4-trifluoromethylphenyl)-piperazine in 40 cm^3 of ethanol, and the mixture is stirred for 30 minutes. Then 2.5 g (0.0155 moles) of 2-chlorobenzyl chloride are added, drop by drop, and the reaction mixture is stirred at room temperature for 20 hours. The inorganic salts are filtered, the filtrate is evaporated to dryness, and the residue dissolved in isopropanol is reacted with hydrogen chloride in isopropanol to form the hydrochloride salt that is suspended in water, filtered, and dried.

3,97 g (62.4 %) of the title compound are obtained as pale drab solids.
M.p.: 216 °C.
Analysis for $C_{18}H_{22}Cl_2F_3N_3O$ (424.297)
calculated: C 50.95%, H 5.23%,
Cl(total) 16.71%,
Cl(ionic) 8.36%, N 9.69%;

found: C 50.74%, H 5.43%,
Cl(total) 17.15%,
Cl(ionic) 8.51%, N 9.69%.

Example 45
1-Benzyl-4-(2,6-dinitro-4-carboxyphenyl)-piperazine

13.8 g (0.1 moles) of potassium carbonate are added to a solution of 17.6 g (0.1 moles) of benzylpiperazine in 100 cm^3 of ethanol, and the mixture is stirred at room temperature for 30 minutes. Then 21.1 g (0.1 moles) of 4-chloro-3,5-dinitrobenzoic acid are added, and the reaction mixture is refluxed for 20 hours. The inorganic salts are filtered, the filtrate is evaporated, the residue is dissolved in 250 cm^3 of water, and acidified with acetic acid. The crystals formed are filtered, and washed with water.

26.0 g (67.4 %) of the title compound are obtained as yellow solids.
M.p.: 279-280 ^oC.
Analysis for $C_{18}H_{18}N_4O_6$ (386.367)
calculated: C 55.96%, H 4.70%, N 14.50%;
found: C 55.35%, H 4.76%, N 14.58%.

Example 46
1-Benzyl-4-(2,6-diamino-4-carboxyphenyl)-piperazine hydrochloride

A solution of 19.32 g (0.05 moles) of

1-benzyl-4-(2,6-dinitro-4-carboxyphenyl)-piperazine in 700 cm^3 of ethanol is acidified with hydrogen chloride in ethanol, and 2.0 g of palladium/carbon (Selcat Q) catalyst are added, then hydrogenized at 30 °C under 10^6 Pa pressure. The suspension is boiled with methanol, and the catalyst is filtered. On cooling, white crystals separate from the filtrate.

15.85 g (87.4 %) of the title compound are obtained. M.p.: 205 °C.

Analysis for $C_{18}H_{23}ClN_4O_2$ (362.860)

calculated: C 59.58%, H 6.39%, Cl(ionic) 9.77%, N 15.44%;

found: C 56.68%, H 6.36%, Cl(ionic) 9.77%, N 15.20%.

Example 47

1-Benzyl-4-(2-formyl-3-chlorophenyl)piperazine

27.6 g (0.2 moles) of potassium carbonate are added to a solution of 17.63 g (0.1 moles) of benzylpiperazine in 100 cm^3 of ethanol, and the mixture is stirred for 30 minutes. Then 15.9 g (0.1 moles) of 2-chloro-6-fluoro-benzaldehyde are added, and the reaction mixture is stirred at room temperature for 30 hours. The inorganic salts are filtered, the filtrate is evaporated. The residue is treated with acetone, any further inorganic salts that separate are filtered, and the organic solution is evaporated. The residual

oil crystallizes on standing.

21.3 g (67.8 %) of the title compound are obtained as light drab solids.

M.p.: 60-61 °C.

Analysis for $C_{18}H_{19}ClN_2O$ (314.814)

calculated: C 68.68%, H 6.08%, Cl 11.26%, N 8.90%;

found: C 68.06%, H 6.15%, Cl 11.38%, N 8.90%.

Example 48

1-(2-Chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride

5.95 g (0.02 moles) of 2-chlorobenzyl-homopiperazine dihydrochloride are dissolved in 50 cm^3 of dimethyl formamide, and, to the solution obtained, 5.52 g (0.04 moles) of potassium carbonate and 0.5 g (0.003 moles) of potassium iodide are added. The mixture is stirred at room temperature for 30 minutes, then 3.73 g (0.02 moles) of 5-chloro-2--methyl-4-nitroaniline are added. The reaction mixture is stirred at 120 to 130 °C for 40 hours. After cooling with ice, the inorganic salts are filtered, the filtrate is evaporated, the residual oil is purified by column chromatography using a mixture of 100 volumes of chloroform and 1 volume of methanol as the eluent. The fractions containing the pure product are evaporated, the residue is dissolved in ethanol and reacted with about tenfold excess of hydrogen chloride in ethanol

under ice cooling to form the dihydrochloride salt.

4.12 g (45.8 %) of the title compound are obtained as yellow crystals.
M.p.: 188-190 °C.
Analysis for $C_{19}H_{25}Cl_3N_4O_2$ (447.796)
calculated: C 50.96%, H 5.63%,
Cl(total) 23.75%, N 12.51%;
found: C 50.29%, H 5.76%,
Cl(total) 23.35%, N 12.27%.

Example 49
1-(4-Fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride

5.62 g (0.02 moles) of 1-(4-fluorobenzyl)-homopiperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro-2--methyl-4-nitroaniline in the presence of 5.52 g (0.04 moles) of potassium carbonate and 0.5 g (0.003 moles) of potassium iodide for 36 hours according to the method described in Example 48. The crude product obtained is purified by flash chromatography using a mixture of 93 volumes of chloroform and 7 volumes of methanol as the eluent. The base is converted to the dihydrochloride salt as described in Example 48.

4.93 g (57.1 %) of the title compound are obtained as yellow crystals.
M.p.: 220-223 °C.
Analysis for $C_{19}H_{25}Cl_2FN_4O_2$ (431.341)

calculated: C 52.91 %, H 5.84%, Cl 16.44%,
N 12.99%;
found: C 52.39%, H 5.94%, Cl 16.31%,
N 12.72%.

Example 50

1-(3-Methoxybenzyl)-4-(5-amino-4-methyl-2--nitrophenyl)homopiperazine dihydrochloride

4.96 g (0.02 moles) of 1-(3-methoxybenzyl)homopiperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro-2-methyl-4-nitroaniline in the presence of 5.52 g (0.04 moles) of potassium carbonate and 0.5 g (0.003 moles) of potassium iodide for 40 hours according to the method described in Example 48. The crude product is purified by column chromatography using a mixture of 100 volumes of chloroform and 1 volume of methanol as the eluent.

5.1 g (57.5 %) of the title compound are obtained as yellow crystals.

M.p.: 173-174 °C.

Analysis for $C_{20}H_{28}Cl_2N_4O_3$ (443.377)

calculated: C 54.18%, H 6.37%, Cl 15.99%,
N 12.64%;
found: C 53.10%, H 6.49%, Cl 16.00%,
N 12.25%.

Example 51

1-Benzyl-4-(5-amino-4-methyl-2-nitrophenyl)-homopiperazine dihydrochloride

5.26 g (0.02 moles) of 1-benzyl-homopiperazine dihydrochloride are reacted with 3.73 g (0.02 moles) of 5-chloro--2-methyl-4-nitroaniline in the presence of 5.52 g (0.04 moles) of potassium carbonate and 0.5 g (0.003 moles) of potassium iodide for 40 hours according to the method described in Example 48. The crude product is purified by column chromatography using a mixture of 100 volumes of chloroform and 1 volume of methanol as the eluent.

5.25 g (60.7 %) of the title compound are obtained as orange solids. M.p.: 214 °C.
Analysis for $C_{19}H_{26}Cl_2N_4O_2$ (413.351)
calculated: C 55.21%, H 6.34%, Cl 17.15%, N 13.55%;
found: C 54.55%, H 6.42%, Cl 16.82%, N 12.99%.

Example 52
1-(2-Fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride

11.04 g (0.08 moles) of potassium carbonate and 1 g (0.006 moles) of potassium iodide are added to a solution of 11.25 g (0.04 moles) of 1-(fluorobenzyl)-homopiperazine dihydrochloride in 150 cm^3 of dimethyl formamide, and the mixture is stirred at room temperature for 30 minutes. Then 7.46 g (0.04 moles) of 5-chloro--2-methyl-4-nitroaniline are added, and the

reaction mixture is stirred at 120 to 130 ^{o}C for 40 hours. After cooling with ice, the inorganic salts are filtered, the filtrate is evaporated, the residue is dissolved in 50 cm^3 of chloroform, the organic solution obtained is extracted 3 times using 20 cm^3 of water each time, the organic phase is dried over anhydrous magnesium sulfate, and evaporated. The residual oil is dissolved in 100 cm^3 of ethanol, and reacted with about tenfold excess of hydrogen chloride in ethanol to form the dihydrochloride salt.

10.43 g (60.45 %) of the title compound are obtained as orange crystals.

M.p.: 204-207 ^{o}C.

Analysis for $C_{19}H_{25}Cl_2FN_4O_2$ (431.341)

calculated: C 52.91%, H 5.84%, Cl 16.44%, N 12.99%;

found: C 52.05%, H 5.96%, Cl 16.21%, N 13.09%.

Example 53

1-(3-Fluorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride

8.43 g (0.03 moles) of 1-(3-fluorobenzyl)-homopiperazine dihydrochloride are reacted with 5.5 g (0.03 moles) of 5-chloro--2-methyl-4-nitroaniline in the presence of 8.28 g (0.06 moles) of potassium carbonate and 0.75 g (0.0045 moles) of potassium iodide according to the method described in Example

52.

6.28 g (48.52 %) of the title compound are obtained as yellow crystals.
M.p.: 202 °C.
Analysis for $C_{19}H_{25}Cl_2FN_4O_2$ (431.341)
calculated: C 52.91%, H 5.84%, Cl 16.44%, N 12.99%;
found: C 53.25%, H 5.90%, Cl 16.01%, N 12.40%.

Example 54
1-(3-Trifluoromethylbenzyl)-4-(5-amino-4--methyl-2-nitrophenyl)homopiperazine dihydrochloride

13.24 g (0.04 moles) of 1-formyl-4--(3-trifluoromethylbenzyl)homopiperazine dihydrochloride are reacted with 7.46 g (0.04 moles) of 5-chloro-2-methyl-4-nitroaniline in the presence of 11.04 g (0.08 moles) of potassium carbonate and 1 g (0.006 moles) of potassium iodide according to the method described in Example 52. Thus, 9.29 g (48.25 %) of the title compound are obtained as yellow crystals. M.p.: 179-181 °C.
Analysis for $C_{20}H_{25}Cl_2F_3N_4O_2$ (481.349)
calculated: C 49.91%, H 5.24%, Cl 14.73%, N 11.64%;
found: C 49.58%, H 5.15%, Cl 14.39%, N 11.81%.

Example 55

1-(4-Methyl-3-nitrobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)piperazine dihydrochloride

12.36 g (0.04 moles) of 1-(4-methyl--3-nitrobenzyl)piperazine dihydrochloride are reacted with 7.46 g (0.04 moles) of 5-chloro-2-methyl-4-nitroaniline in the presence of 11.04 g (0.08 moles) of potassium carbonate and 1 g (0.006 moles) of potassium iodide according to the method described in Example 52.

7.00 g (38.18 %) of the title compound are obtained as orange crystals.

M.p.: 232-234 °C.

Analysis for $C_{19}H_{25}Cl_2N_5O_4$ (458.348)

calculated: C 49.79%, H 5.50%, Cl 15.47%, N 15.28%;

found: C 50.00%, H 5.55%, Cl 15.36%, N 15.05%.

Example 56

1-(3-Chlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride

11.9 g (0.04 moles) of 3-chlorobenzyl-homopiperazine dihydrochloride are reacted with 7.46 g (0.04 moles) of 5-chloro-2--methyl-4-nitroaniline in the presence of 11.04 g (0.08 moles) of potassium carbonate and 1 g (0.006 moles) of potassium iodide according to the method described in Example

52.

7.3 g (40.76 %) of the title compound are obtained as orange crystals.

M.p.: 187-188 °C.

Analysis for $C_{19}H_{25}Cl_3N_4O_2$ (447.798)

calculated: C 50.96%, H 5.63%, Cl 23.75%, N 12.51%;

found: C 51.33%, H 5.61%, Cl 23.59%, N 12.26%.

Example 57

1-(3-Cyanobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine monohydrochloride

11.49 g (0.04 moles) of 1-(3-cyanobenzyl)homopiperazine dihydrochloride are reacted with 7.46 g (0.04 moles) of 5-chloro-2-methyl-4-nitroaniline in the presence of 11.04 g (0.08 moles) of potassium carbonate and 1 g (0.006 moles) of potassium iodide according to the method described in Example 52.

4.33 g (30.05 %) of the title compound are obtained as yellow crystals.

M.p.: 214-216 °C.

Analysis for $C_{20}H_{24}ClN_5O_2$ (401.900)

calculated: C 59.77%, H 6.02%, Cl 8.82%, N 17.43%;

found: C 59.75%, H 6.05%, Cl 8.82%, N 16.93%.

Example 58

1-(2,6-Dichlorobenzyl)-4-(5-amino-4-methyl-2-nitrophenyl)homopiperazine dihydrochloride

13.0 g (0.04 moles) of 1-(2,6-dichlorobenzyl)homopiperazine dihydrochloride are reacted with 7.46 g (0.04 moles) of 5-chloro-2-methyl-4-nitroaniline in the presence of 11.04 g (0.08 moles) of potassium carbonate and 1 g (0.006 moles) of potassium iodide according to the method described in Example 52.

7.5 g (38.88 %) of the title compound are obtained as orange crystals.

M.p.: 185-186 °C.

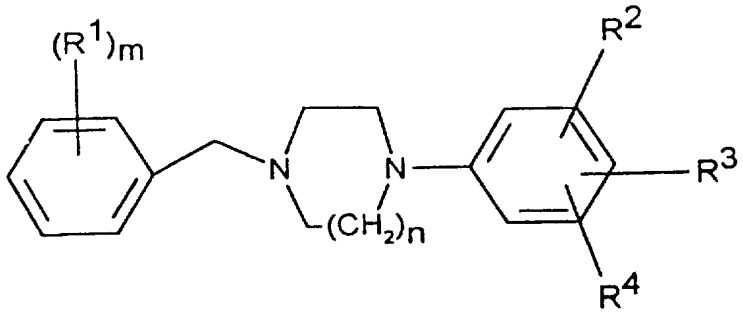
Analysis for $C_{19}H_{24}Cl_4N_4O_2$ (482.239)

calculated: C 47.32%, H 5.05%, Cl 29.41%, N 11.62%;

found: C 46.53%, H 5.02%, Cl 30.34%, N 11.58%.

Claims

1. A piperazine derivative of the formula



I

wherein

R^1 stands for a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trihalomethyl group, a nitro group or an amino group which latter can be substituted by a C_{1-4} alkyl group, and

n has a value of 1 or 2, or

R^1 represents a cyano group, and

n has a value of 2,

m is 0, 1, 2 or 3,

R^2, R^3 and R^4 mean, independently, a hydrogen, a halo, a trihalomethyl group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a nitro group, a carboxy group, a formyl group, a hydroxy group or an amino group which latter can be substituted by a C_{1-4} alkyl group,

and a pharmaceutically acceptable acid addition salt thereof.

2. A compound of the formula I as claimed in Claim 1, wherein

R^1 stands for a halo, a C_{1-4} alkyl group,

a C_{1-4} alkoxy group, a nitro group or a trifluoromethyl group,

m is 0, 1 or 2,

R^2, R^3 and R^4 mean, independently, a hydrogen, a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trifluoro methyl group, a nitro group; an amino group, a formyl group or a carboxy group,

n is 1 or 2,

and a pharmaceutically acceptable acid addition salt thereof.

3. A compound of the formula I as claimed in Claim 1 or 2, wherein

R^1 stands for a chloro, a fluoro, a methyl group, a methoxy group, a nitro group or a trifluoromethyl group,

m is 0, 1 or 2,

R^2, R^3 and R^4 mean, independently, a hydrogen, a chloro, a methyl group, a methoxy group, a trifluoromethyl group, a nitro group, an amino group, a formyl group or a carboxy group,

n is 1 or 2,

and a pharmaceutically acceptable acid addition salt thereof.

4. A compound of the formula I as claimed in any of Claims 1 to 3, wherein

R^1 stands for a chloro, a fluoro, a methyl group or a methoxy group,

m is 0 or 1,

R^2, R^3 and R^4 means, independently, a hydrogen, a chloro, a methyl group, a methoxy group,

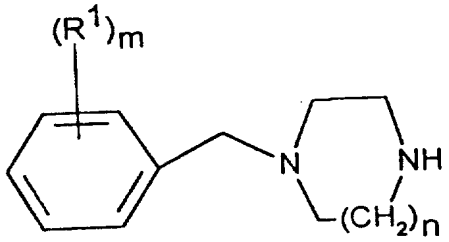
a trifluoromethyl group, a nitro group, an amino group or a formyl group,

n is 1,

and a pharmaceutically acceptable acid addition salt thereof.

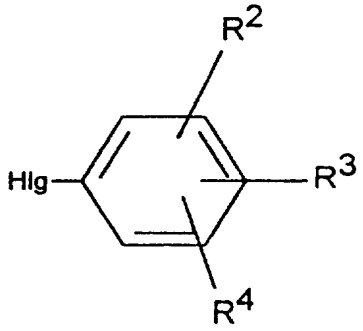
5. A process for preparing a piperazine derivative of the formula I, wherein R^1, R^2, R^3, R^4, m and n are as defined in Claim 1, or a pharmaceutically acceptable acid addition salt thereof, in which

a) a 1-benzylpiperazine derivative of the formula



II

wherein R^1, m and n are as stated in relation to the formula I, is reacted with an aromatic halo compound of the formula

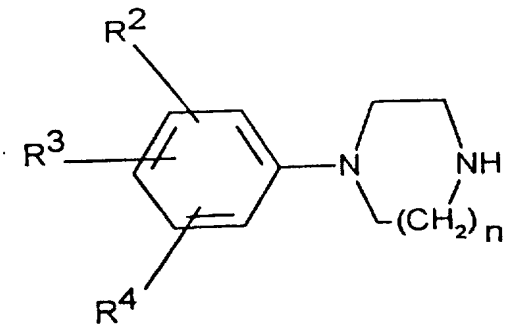


III

wherein R^2, R^3 and R^4 are as stated in relation to the formula I, Hlg represents a chloro

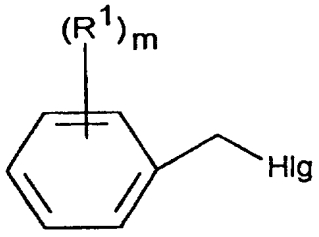
or bromo atom; or

b) a 1-phenylpiperazine derivative of the formula



IV

wherein R^2, R^3, R^4 and n are as stated in relation to the formula I, is reacted with a benzyl halide of the formula



V

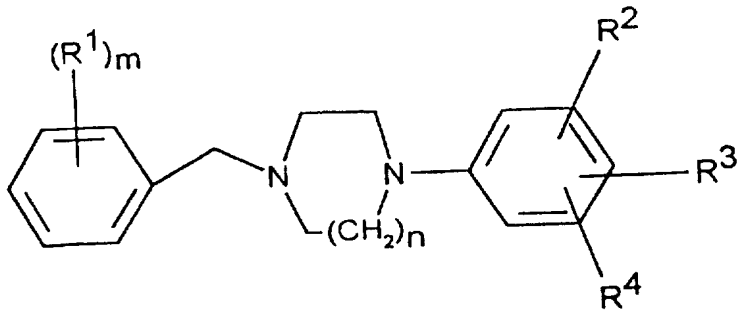
wherein R^1 and m are as stated in relation to the formula I, Hlg represents a chloro or bromo atom;

and, if desired, an obtained compound of the formula I is converted to a pharmaceutically acceptable acid addition salt thereof;

or, if desired, an obtained compound of the formula I, wherein one or more of R^1, R^2, R^3 and R^4 stand(s) for a nitro group, m and n are as stated above, is catalytically

hydrogenized to obtain a corresponding amino compound.

6. A pharmaceutical composition comprising a piperazine derivative of the formula



wherein

R^1 stands for a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trihalomethyl group, a nitro group or an amino group which latter can be substituted by a C_{1-4} alkyl group, and

n has a value of 1 or 2, or

R^1 represents a cyano group, and

n has a value of 2,

m is 0, 1, 2 or 3,

R^2, R^3 and R^4 mean, independently, a hydrogen, a halo, a trihalomethyl group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a nitro group, a carboxy group, a formyl group, a hydroxy group or an amino group which latter can be substituted by a C_{1-4} alkyl group,

or a pharmaceutically acceptable acid addition salt thereof as the active ingredient and one or more usual carrier(s).

7. A pharmaceutical composition as claimed

in Claim 6 in which the active ingredient is a piperazine derivative of the formula I, wherein

R^1 stands for a chloro, a fluoro, a methyl group, a methoxy group, a nitro group or a trifluoromethyl group,

m is 0, 1 or 2,

R^2, R^3 and R^4 mean, independently, a hydrogen, a chloro, a methyl group, a methoxy group, a trifluoromethyl group, a nitro group, an amino group, a formyl group or a carboxy group,

n is 1 or 2,

or a pharmaceutically acceptable acid addition salt thereof.

8. A pharmaceutical composition as claimed in Claim 6 or 7 in which the active ingredient is a piperazine derivative of the formula I, wherein

R^1 stands for a chloro, a fluoro, a methyl group or a methoxy group,

m is 0 or 1,

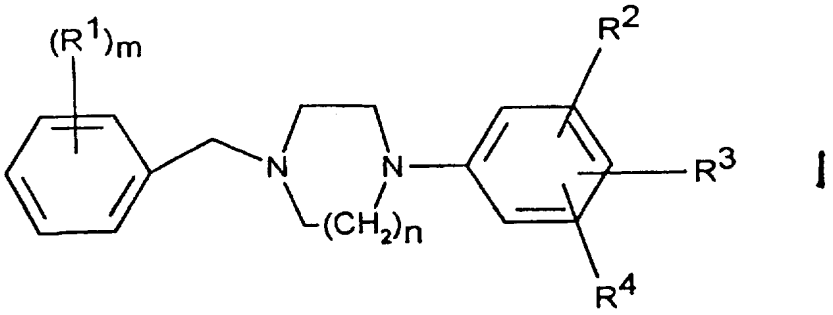
R^2, R^3 and R^4 means, independently, a hydrogen, a chloro, a methyl group, a methoxy group, a trifluoromethyl group, a nitro group, an amino group or a formyl group,

n is 1,

or a pharmaceutically acceptable acid addition salt thereof.

9. A medical treatment process in which a patient suffering especially in a disease of the central nervous system is treated with

a therapeutically active, non-toxic quantity of a piperazine derivative of the formula



I

wherein

R^1 stands for a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trihalomethyl group, a nitro group or an amino group which latter can be substituted by a C_{1-4} alkyl group, and

n has a value of 1 or 2, or

R^1 represents a cyano group, and

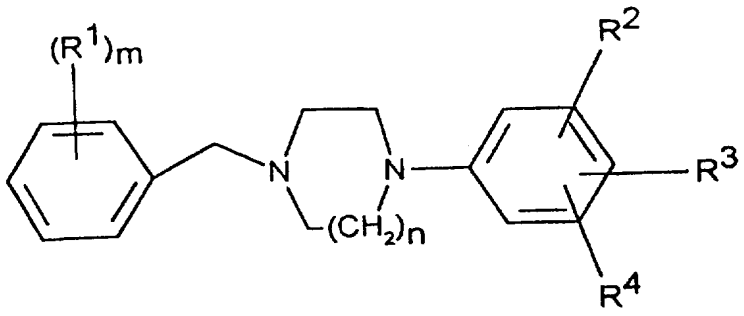
n has a value of 2,

m is 0, 1, 2 or 3,

R^2, R^3 and R^4 mean, independently, a hydrogen, a halo, a trihalomethyl group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a nitro group, a carboxy group, a formyl group, a hydroxy group or an amino group which latter can be substituted by a C_{1-4} alkyl group,

or a pharmaceutically acceptable acid addition salt thereof.

10. The use of a piperazine derivative of the formula



I

wherein

R^1 stands for a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trihalomethyl group, a nitro group or an amino group which latter can be substituted by a C_{1-4} alkyl group, and

n has a value of 1 or 2, or

R^1 represents a cyano group, and

n has a value of 2,

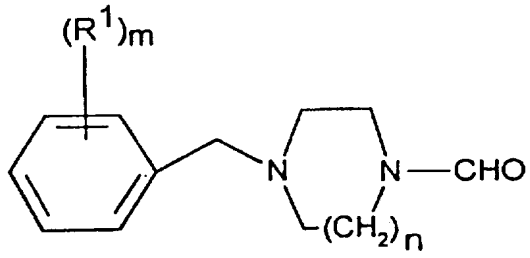
m is 0, 1, 2 or 3,

R^2, R^3 and R^4 mean, independently, a hydrogen, a halo, a trihalomethyl group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a nitro group, a carboxy group, a formyl group, a hydroxy group or an amino group which latter can be substituted by a C_{1-4} alkyl group,

or a pharmaceutically acceptable acid addition salt thereof, optionally in admixture with one or more carrier(s) commonly used in pharmaceutical compositions, for preparing medicaments having an activity in the treatment of diseases especially due to pathological alterations of the central nervous system.

11. A 1-benzyl-4-formylpiperazine

derivative of the formula



VI

wherein

R^1 stands for a halo, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a trifluoromethyl group or a nitro group,

m has a value of 0, 1, 2 or 3,

n has a value of 1 or 2.